REMARKS

4. As requested, attached is an abstract on a separate sheet.

5. The hyperlinks on pages 13 and 24 of the specification have been deleted.

6. Claims 1, 7, and 8 have been amended as suggested.

7. The claims stand rejected under §§101, and 112, first paragraph.

The claimed GPCR ("HGRL101") is a new form of the relaxin receptor. Relaxin has been described as "a hormone important for the growth and remodeling of reproductive and other tissues during pregnancy." See, Hsu et al., *Science*, 295:671 (Abstract). Its activity includes "promotion of growth and dilation of the cervix," making it an important target for the treating conditions associated with labor and pregnancy. ("Preterm labor and delivery remain major obstetrical problems. Studies on relaxin receptors could allow the design of agonistic or antagonistic relaxin analogs for the treatment of disorders of labor onset." Hsu et al., *ibid*, Page 673, Column 3.) Relaxin and its receptor have a well-established physiological role in the body, and therefore a substantial, credible, and specific utility, e.g., to modulate cervical ripening and labor induction.

There is adequate information to establish that the HGRL101 is a relaxin receptor. For example, it is expressed in the uterus, as is LGR7 and LGR8 – other representatives of the relaxin receptor family. See, Hsu et al., *ibid*, Page 672, Columns 2-3.

In addition, the sequence identity between HGRL101 and LGR7 is adequate to define it as a member of the relaxin receptor family. As shown in Exhibit 1 (QUERY is HGRL101 sequence), HGRL101 shares about 94% sequence identity and 95% sequence similarity with LGR7, far greater than the about 55% sequence identity between LGR7 and LGR8 (Exhibit 2: QUERY is LGR7 sequence;). LGR7 and LGR8 – as admitted in the Office action – have been shown to have relaxin

binding properties. See, e.g., Hsu et al., *ibid*, Fig. 1 (A and B). Given that HGRL101 has even higher similarity to LGR7, there is no reasonable basis to deny that it would also possess relaxin receptor properties.

In the Patent Office's *Utility Guideline Training Materials*, Example 10 (attached for the examiner's convenience) describes an isolated DNA that coded for a protein having 95% similarity (the same amount as shown here) to a known ligase, and the Patent Office considered that value sufficient to accept the applicant's assertion that the protein possessed ligase activity ("there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase"), even though the activity had not been experimentally demonstrated. Similarly, the HGHRL101 polypeptide has sufficient sequence similarity to other relaxin receptors (indeed, the same 95% as with the PTO's ligase example), and under the same reasoning provided in Example 10 of the *Guidelines*, and relied upon by applicant, the rejection should be withdrawn.

12. It is stated in the Office action that the specification does not contain a written description of variants and fragments.

On Page 21 of the specification, the definitions of "fragment" and "variant" are provided. Preferred sizes of fragments are also disclosed on, e.g., Page 3, lines 19-29, Page 7, lines 22-26, etc. As the definition indicates, these fragments and variants are defined as characteristic of HGRL101, e.g., retaining a biological activity (e.g., an immunogenic activity or relaxin activity). These fragments can be made routinely. Similarly, variants of HGRL101 can also be made routinely, e.g., Page 21, lines 6-32, and then screened for activity (e.g., Pages 16-17; Examples 2-4). Examples of making variants is described in the specification, e.g., on Page 21 where conservative substitutions have been disclosed.

The claims have been amended to clarify that the polypeptide fragments are "immunospecific" for HGR101. Support for the amendment can be found in the specification, e.g. Page 14, lines 1-7. The claims have also been amended to clarify that the polynucleotide fragments

are specific for HGRL101 ("gene-specific"). Support for the amendment is at, e.g., Page 8, lines 24-25, of the specification.

13. Various claims are rejected under 112, second paragraph as being indefinite.

Claims 1, 4, 6-9, and 11 are rejected, allegedly because the recitation of "fragments and variants" is indefinite. As mentioned above, the phrase "fragments and variants" is defined in the specification, and therefore, when the claims are read in light of the specification, would be understood by the skilled worker.

Claims 1, 7, 8, and 9 have been clarified by reciting the particular nucleotide positions from which the encoded polypeptide is translated.

Claim 6 has been amended to provide antecedent basis to the term "expression vector."

Claims 7 and 8 has been amended by deleting the redundancy.

Claim 11 has been amended by deleting step (f). New claim 12 has been added which is dependent on claim 11, and which incorporates its method.

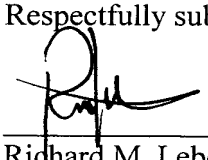
Claim 4 has been amended by reciting the conditions under which stringent hybridization is achieved. Support for this amendment can be found in the specification, e.g., Page 7, lines 34-37.

14-15. As indicated above, "fragments and variants" is clearly defined in the specification (e.g., Page 21) in such a way that the polynucleotides and polypeptides of U.S. Pat. No. 5,756,309 would be excluded. Therefore, the rejection should be withdrawn

In that this is a full and complete response to the Office Action of March 6, 2003, Applicant respectfully requests that this application be allowed and passed to issue. If the Examiner for any reason feels that a personal conference with Applicant's Attorneys might expedite prosecution of this application, the Examiner is respectfully requested to telephone the undersigned locally.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No.: MERCK-2034

Date: September 3, 2003

RML/jmj

REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS

Contents

characterize the protein. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have asserted or identified specific and substantial utilities. The research contemplated by Applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Claim 1 is also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Example 10: <u>DNA Fragment encoding a Full Open Reading Frame (ORF)</u>

Specification: The specification discloses that a cDNA library was prepared from human kidney epithelial cells and 5000 members of this library were

sequenced and open reading frames were identified. The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.

Claim 1: An isolated and purified nucleic acid comprising SEQ ID NO: 2.

Analysis: The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently the answer to the question is yes.

EXHIBIT 1

>gi|11056007|ref|NM_021634.1| LWG Homo sapiens leucine-rich repeat-containing G protein-coupled
receptor 7 (LGR7), mRNA
Length = 2274

Score = 841 bits (424), Expect = 0.0
Identities = 465/475 (97%), Gaps = 4/475 (0%)
Strand = Plus / Plus

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>gi|10441729|gb|AF190500.1|AF190500 LU Homo sapiens leucine-rich repeat-containing G protein-coupled
receptor 7 (LGR7) mRNA, complete cds
Length = 2274

Score = 841 bits (424), Expect = 0.0
Identities = 465/475 (97%), Gaps = 4/475 (0%)
Strand = Plus / Plus

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>gi|11056008|ref|NP_067647.1| leucine-rich repeat-containing G protein-coupled receptor 7 [Homo sapiens]

gi|21362643|sp|Q9HBX9|LGR7_HUMAN Relaxin receptor 1 (Leucine-rich repeat-containing G protein-coupled receptor 7)

gi|10441730|gb|AAG17167.1| leucine-rich repeat-containing G protein-coupled receptor 7 [Homo sapiens]

Length = 757

Score = 250 bits (638), Expect(2) = 4e-75
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Frame = +1

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           TDALCWIPIFV K LSLLQVEIPGTITSWVVI    INSALNPILYTLTTRPFKEMIHRF
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>gi|18677729|ref|NP_570718.1| G protein coupled receptor affecting testicular descent [Homo sapiens]

gi|21362625|sp|Q8WXD0|LGR8_HUMAN Relaxin receptor 2 (Leucine-rich repeat-containing G protein-coupled receptor 8) (G protein-coupled receptor affecting testicular descent)

gi|18483168|gb|AAL73946.1|AF453828_1 G protein-coupled receptor affecting testicular descent [Homo sapiens]

gi|18702460|gb|AAL69324.2|AF403384_1 LGR8 [Homo sapiens]

Length = 754

Score = 155 bits (391), Expect = 3e-37
Identities = 75/127 (59%), Positives = 100/127 (78%)
Frame = +1

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           +CWIP+FV K LSL +VEIP T+TSW+VI +  +NSALNPILYTLTT  FK+ + +  H
Sbjct: 649 ICWIPVFVVKILSLFRVEIPDTMTSWIVIFFLPVNSALNPILYTLTTNFFKDKLKQLLHK 708

Query: 370 YRQRKSM 390
           + QRKS+
Sbjct: 709 H-QRKSI 714
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EXHIBIT 2

>gi|18677729|ref|NP_570718.1| G protein coupled receptor affecting testicular descent [Homo sapiens]

gi|21362625|sp|Q8WXD0|LGR8_HUMAN Relaxin receptor 2 (Leucine-rich repeat-containing G protein-coupled receptor 8) (G protein-coupled receptor affecting testicular descent)

gi|18483168|gb|AAL73946.1|AF453828_1 G protein-coupled receptor affecting testicular descent [Homo sapiens]

gi|18702460|gb|AAL69324.2|AF403384_1 LGR8 [Homo sapiens]

Length = 754

Score = 756 bits (1953), Expect = 0.0
Identities = 394/716 (55%), Positives = 520/716 (72%), Gaps = 11/716 (1%)

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Query: 66  NGWSMQFDKYFASYYKMTSQYPFEAETPECLVGSVPVQCLCQGLELDCDETNLRAVPSVS 125
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